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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,503	06/28/2007	Helen Blau	STAN-327	7009
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EXAMINER				
WOLLENBERGER, LOUIS V				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/581,503

Applicant(s)

BLAU ET AL.

Examiner

Louis Wollenberger

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2008.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 and 34 is/are pending in the application.
4a) Of the above claim(s) 9, 11 and 17-26 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-8, 10, 12-16 and 34 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 01 June 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 11/14/2007.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claim(s) 1-16 and 34, drawn to a method of producing short hairpin RNA, comprising ligating a linker nucleic acid to a dsDNA to produce an intermediate nucleic acid, and converting said intermediate nucleic acid to a linear dsDNA, and to a system comprising reagents used in said method, in the reply filed on 11/21/2008 is acknowledged. Applicant further elects the method thereof according to claims 10 and 12.

The traversal is on the ground(s) that it would not be unduly burdensome to examine all pending claims in the same application. This is not found persuasive because burden is not a factor for consideration in a Requirement for Unity of Invention in a national stage application (MPEP 802 and 1850).

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-26 and 34, filed by preliminary amendment on 6/28/07, are pending.

Claims 9, 11, and 17-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-8, 10, 12-16, and 34 are examined herein.

Application Data Sheet/Oath or Declaration

The Examiner notes a discrepancy in the spelling of the last name of one of the Applicants, Jason Myers or Meyers, as provided on the Application Data Sheet and in the Oath or Declaration, filed 6/1/2006 and 6/28/2006, respectively. The ADS spells the name Meyers,

while the Declaration spells the name Myers. Applicant will note the name has been spelled Meyers in the Filing Receipt or Bibliographic Data Sheet produced by the Office and on the Pre-Grant Application Publication, US 20080021205 A1. Applicant is requested to review and verify the spelling and, if appropriate, make the necessary corrections, including a request for corrected filing receipt.

Claim Objections

Claim 1 is objected to because of the term "hRNA." The term is defined neither by the claims nor the specification and is not a readily recognized term of art. For clarity, it is respectfully requested Applicant spell out the term "hRNA" at its initial use in the claims.

Claim 34 is objected to for depending on a withdrawn claim, claim 17.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10, and 12-16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "said shRNA" in line 3 bridging to 4 and in line 7. There is insufficient antecedent basis for this limitation in the claim. Dependent claims 2-8, 10, and 12-16 are rejected therefor.

Claim 6 is further rejected as being indefinite because the claim recites the limitation "said two or more restriction endonucleases" in line 1 bridging to 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, first paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 7, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn to the method of Claim 1 for producing an hRNA expression module. Claims 2 and 3 further comprise producing an initial dsDNA from a target nucleic acid. While claim 2 is generically drawn to production of dsDNA by any means, claim 3 is more narrowly drawn to production of dsDNA by fragmenting the target nucleic acid. Similarly, Claim 7 requires "size modifying" the resulting intermediate nucleic acid, and is generic with regard to precise means used to size modify the nucleic acid. Claim 34 requires "converting reagents," and therefore embraces the genus of agents that convert an intermediate nucleic acid to a linear dsDNA properly capable of encoding a shRNA specific for a target nucleic acid.

The specification discloses a specific method for creating shRNA expression modules that requires as essential components known restriction enzymes having known activities, resulting in the production of sequence specific overhangs that are said to facilitate the cloning process (see Fig. 1 and corresponding discussion in specification). Moreover, the specification teaches the restriction enzymes used to produce the initial dsDNA are chosen so as to produce fragments of the appropriate size for shRNAs (i.e., on the order of 20 to 21 nts in length) (pages 3 to 4). Accordingly, the specification describes a single method for making shRNA expression modules wherein the restriction endonucleases used and the fragments produced thereby are critical to the method for producing the corresponding module and expression vector. The specification does not describe any other means for producing initial dsDNAs or size modifying intermediate nucleic acids. There is no disclosure of any mechanical means for producing initial dsDNA with characteristics suitable for the claimed cloning method nor for properly size modifying the intermediate nucleic acid to produce the shRNA module with the proper characteristics. There is no disclosure of any chemical means for hydrolyzing genomic DNA or

reverse transcribing mRNA in the manner necessary to produce fragments of dsDNA of the size and with the features necessary to facilitate cloning according to the instant method.

Thus, adequate written description does not exist in the instant application for the genus of methods and converting reagents embraced by instant claims 2, 3, 7, and 34. That is, the specification does not adequately allow persons of ordinary skill in the art to recognize that applicant(s) were in possession of the entire genus of methods as now claimed in the instant claims. The elements and/or means required for the methods are recited in general terms only according to their function only without any description of structure, there is no art-recognized correlation between the structure and function, and the specification does not provide the support needed to enable one skilled in the art to predict with a reasonable degree of confidence the structure of the claimed inventions from a recitation of function.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations. See *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures,

diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

MPEP 2163 states in part that "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. >The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

In the instant case, applicants have not satisfied either of these criteria. That is, the instant application discloses no structures other than specific, known restriction enzymes and the function required by the claims for producing initial dsDNA and size modifying an intermediate nucleic acid in the manner necessary to produce the shRNA expression module. Indeed the

specification teaches that the success of the claimed method depends on the sequence-specific nature of the restriction enzymes used in the method, from the production of complementary 2-nt overhangs to the removal of the intervening loops in the linkers.

While the specification adequately describes enzymatic methods for fragmenting and size modifying it does not adequately describe the entire genus of methods using any means for producing dsDNA or fragmenting nucleic acids or size modifying said intermediate nucleic acids, since the means used is critical to the method of making. Thus, applicants have not shown possession of the full scope of what is now claimed in claims 2, 3, and 7.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 112, first paragraph (enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10, and 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing shRNA expression modules in solution in vitro, does not reasonably provide enablement for methods of producing shRNA expression modules in a cell in culture or in vivo.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

As evidence by instant claim 15, the instantly claimed method for producing a hRNA expression module embraces both in vitro and in vivo embodiments as might occur in a cell in culture or in vivo.

While the instant specification and prior art reasonably enables the production and amplification of hRNA expression constructs in solution using conventional molecular biological techniques and reagents as are typically encountered in the laboratory setting, neither the specification nor the prior art describes or enables any method remotely similar to that now claimed taking place inside a cell in culture, much less in a cell in vivo in a living organism. As

shown by Fig. 1 and the specification as a whole, the invention is directed to a specific recombinant DNA procedure involving several steps that not only require a specific temporal arrangement but particular chemical features to produce the final product encoding a hairpin RNA complementary to a target nucleic acid. The likelihood of such steps taking place in any cell, at least any known cell, is reasonably very low. Moreover, the specification does not exemplify or provide and technical guidance as to how to accomplish the method of claim 13, for example, in a cell. Rather, the instant invention is directed to the use of a series of steps carried out in cell-free solutions, wherein nucleic acids are cut and ligated in specific manners to produce a final construct or set of constructs, such as library, which may then be transfected into a cell. While the final constructs may be transcribed inside a cell, the method as whole could not reasonably take place in the cell, as now claimed. It is reasonable, therefore, to question whether one of skill would have been capable of practicing method in vivo, as asserted in claim 15, without needing to engage in undue experimentation. As there is no direction or guidance showing one of skill how to produce hRNA expression modules in a cell by any of the steps now required, and such methods are not routine in the art, the evidence suggests enabling disclosure was not present at the time of filing enabling one to practice these in vivo embodiments.

Considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8, 13-16, and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by McCampbell et al. (WO 2005/023991).

Citing from US Provisional Application 60/500860, McCampbell et al. taught methods for making small hairpin (shRNA) libraries and expression constructs (pp. 1-32 and Figs. 1-4), comprising enzymatically digesting a cDNA library with one or more restriction endonucleases to produce (initial) dsDNA fragments, ligating the fragments to first and second hairpin (linker) nucleic acids to produce a circular nucleic acid, converting said circular nucleic acid to a linear dsDNA, size modifying said linear dsDNA to remove intervening linker sequences, and cloning the final size modified product into an expression vector to give rise to a module comprising a shRNA coding sequence, which, upon transcription, produces a hairpin RNA corresponding to the initial dsDNA fragments (see Figures and relevant discussion in specification). Multiple different restriction endonucleases are suggested for use, including those such as *Mme* I that cut a suitable number of bases away from the recognition site. Kits (i.e., systems) comprising the

reagents, including the nucleic acid starting materials and restriction enzymes, necessary to synthesize the shRNA library, are also disclosed.

Accordingly, McCampbell et al. anticipates the instantly claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCampbell et al. (WO 2005/023991) as applied to claims 1-8, 13-16, and 34 above, and further in view of Abarzua (WO 01/40516).

McCampbell et al. is relied on for the reasons given above in the rejection under 35 USC 102.

McCampbell et al. does not teach amplifying the circular DNA intermediate prior to converting, size modifying, and cloning said intermediate. More specifically, McCampbell et al. does not teach rolling circle amplification.

Abarzua taught methods for making and amplifying circular DNA containing genomic DNA inserts, comprising generating dsDNA fragments by restriction endonuclease digestion, ligating the dsDNA fragment to first and second hairpin nucleic acids, and then amplifying the circular product using known rolling circle techniques (Fig. 4 and see pages 1-29, such as pages 24 and 25, for example). The method is said to be suitable for amplifying genomic and viral DNA and for generating cDNA libraries (page 24-25). It is said the dsDNA insert may be generated from larger segments using any desired restriction enzyme(s). (page 25). Numerous advantages are associated with the method, including the fact that the sequences are amplified in proportion to their occurrence in the preparation, as well as enabling one to generate and amplify circles directly from starting sources with no size restrictions (page 25 and 26). For example, it is said circles of from 50 to 5000 bases may synthesized and amplified using the technique (page 26).

Thus, the prior art as a whole reasonably suggested the instantly claimed method. One of skill would have had reason to use the rolling circle amplification method of Abarzua as part of

the method of McCampbell et al. to improve the efficiency of the cloning technique, by first amplifying the circular DNA intermediate prior to digestion to produce multiple copies for ligation into the target vector.

Accordingly, in the absence of secondary considerations, the instant method is considered to be prima facie obvious over the prior art as a whole, represented herein by McCampbell et al. and Abarzua.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1635
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